REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 33-36 are requested to be cancelled without prejudice or disclaimer thereto. Claim 37 is currently being amended to recite terms consistent with those used in claim 1. No new matter is added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-32 and 37-71 are now pending in this application, of which claims 8-11 and 47-66 are withdrawn.

Claim Objections

Claims 34-37 have been objected to for allegedly being in improper dependent form and encompassing a broader scope of condensing polymer than presently elected. Without acquiescing to the rejection, claims 34-36 have been canceled, and claim 37 has been amended to fall within the scope of the elected claims. Therefore, withdrawal of the objection is respectfully requested.

Claim Rejections under 35 U.S.C. § 103

Sanford and Balhorn as evidenced by Oard

Claims 1-5, 7, 12-13, 17-20, 22-30, 32-38, 42-45 and 67 were rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Sanford (U.S. Pat. No. 5,204,253) and

Balhorn (*Mol. Reprod. Dev.* (2000) 56:230-234) as evidenced by Oard (*Plant Cell Tissue Organ Culture* (1993) 33:247-250). Applicants respectfully traverse this rejection.

The Supreme Court recently reaffirmed the *Graham* factors for determining obviousness in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727,1739 (2007) (holding that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions). Further, the Court still requires that the reasoning used to combine the elements in the fashion claimed be made explicit. *Id.* at 1740-41.

Sanford described a process and an apparatus that used "cold" gas shock to accelerate particles, which were placed onto planar carrier sheet/resilient membrane for introduction into a suitable target of cells (*see* claim 1). In Example 1, Sanford used M-10 tungsten particles (*see* column 15, line 14). Sanford precipitated nucleic acid onto the particles in the presence of the following ingredients: EDTA, spermidine (N-(3-aminopropyl)butane-1,4-diamine) and calcium chloride, after which the particles were placed onto a resilient membrane prior to administration (*see* column 15, lines 20-22, and in particular lines 37-42). Preparation of the particles and their administration took place on the same day (*see* column 15, lines 45-46).

Oard disclosed the use of tungsten particles (M20 series – ranging in size from 0.5, or M10 series – ranging is size from 3.0 μm or 0.3 to 2.1 μm) or gold "flakes" (ranging in size from 1 to 3 μm), where the particles were coated with DNA in the presence of spermidine and calcium chloride (*see* page 249, 1st col., 3rd paragraph and paragraph bridging both columns). Oard described the transient gene-expression in monocots (a plant that has only one cytoledon such as corn seed).

Noteably, neither Sanford nor Oard taught or suggested the use of a homopolymer of arginine in any capacity. Likewise, neither reference taught nor suggested altering ingredients or substituting any ingredients as a way to increase attachment of a nucleic acid onto particles and/or increase stability of coated particles.

Balhorn provided an analysis of DNA condensation using protamine (small arginine-rich proteins that were attached to DNA towards the end of sperminogenesis) and arginine-rich peptides by examining toroid (coiling of DNA) stability. Specifically, using decondensation (release of DNA) experiments, the authors showed that an increase in stability of toroids could lead to an increase in uptake by somatic cells and sperm cells. The authors concluded that the arginine content of protamine-related sequences could have an effect on their rate of dissociation from DNA. Thus, Balhorn taught a method for identifying analogues of protamine that could be bound to DNA and increase the efficacy of the DNA's uptake by sperm and other cells (*see* abstract, last sentence). The authors also suggested that faster release of protamine from DNA, and thus cell uptake, could be achieved by using small polymers of polyarginine and specifically, a protein containing a domain with fewer than 12 arginine residues (*see* page 233, 2nd col., 3rd sentence from bottom).

In other words, Balhorn related to using an arginine-rich peptide or protein to increase uptake of DNA by cells. It did not mention nor suggest the use of such moieties in the context of attaching DNA molecules to inert particles. Balhorn provided no suggestion that the addition of any arginine moiety would be desirable when attaching DNA onto particles, let alone that it could benefit the DNA in physically attaching itself to inert particles and/or increase its stability while being attached.

The KSR Examination Guidelines published by the Office explicitly state that

> the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge.

(72 Fed. Reg. 5726, 5727 (O.G. 2007)). The Guidelines go on to emphasize the importance of articulating the reasoning behind combining the cited references. *See also KSR,* 127 S.Ct. at 1740-41.

In this case, the Examiner has provided no rationale as to why the transfection methods of Balhorn would have reasonably been expected to be compatible with the deposition of DNA onto inert metal carrier particles using a homopolymer of arginine and an

inert metal ion chelating agent as presently claimed. In fact, Balhorn does not mention nor even suggest the idea of attaching DNA to inert metal carrier particles.

The presently claimed invention is far more than a predictable use of known elements. The combination of cited references would not have reasonably been expected to yield the inventive particles. None of the cited documents would have led a person of skill in that art to believe that the addition of an arginine moiety instead of spermidine, let alone a homopolymer comprising Arg_2 to Arg_{10}, together with DNA, particles and a chelating agent, such as EDTA, could improve the physical attachment of DNA to particles and thus stability of the composition. Instead, based on the teachings of Balhorn, at best the skilled person would have been motivated to use other arginine moieties to improve transfection efficiency of cells. He/she would have selected arginine moieties that released DNA more readily (rather than attached more stably) as a means to increase cellular uptake of the DNA.

Applicants submit that even if a skilled person was to combine the teachings of the cited documents, he/she would have had no expectation that a combination of a homopolymer comprising Arg_2 to Arg_{10}, together with DNA, particles and a chelating agent could improve the physical attachment of DNA to inert particles and thus stability of the composition, thereby making it suitable for use as per the present invention. Thus, the cited references, alone or in combination, cannot render the present claims unpatentable.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Sanford and Balhorn as evidenced by Oard and in further view of Cherng

Claims 1-5, 7, 12-15, 17-30, 32-40, 42-46 and 67 were rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Sanford and Balhorn as evidenced by Oard and in further view of Cherng (*Pharm. Res.* (1999) 16:1417-1423). Applicants respectfully traverse this rejection for at least the reasons previously discussed and those that follow.

The Examiner has further characterized Oard as teaching the use of gold particles to reduce particle clumping and has stated that Cherng teaches that condensation of nucleic

acids with cationic polymers is stabilized by the presence of sucrose. Applicants disagree with this characterization.

In addition to the comments above, Applicants point out that Oard discussed the problem of "severe clumping" when making the DNA-microcarriers, and how the authors failed to solve this problem. Specifically, on page 249, 2nd col., Oard states that the "use of gold flakes and poly-L-lysine did reduce clumping relative to tungsten particles, but did not eliminate the problem entirely."

Cherng studied the stability of polymer-plasmid complexes (polyplexes) in an aqueous dispersion and in a lyophilised form. The polymer used by the authors is termed poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA), a water-soluble cationic polymer. PDMAEMA was able to bind to DNA by electrostatic interactions. In addition, at a polymer/plasmid ratio of above 2 (w/w), positively charged polyplexes formed with an average size of around 0.2 μm. These particular polyplexes could be used to transfect cells.

In other words, Cherng used PDMEAMA-pCMV lacZ plasmid complexes (polyplexes). The authors showed that these polyplexes were relatively stable when stored in aqueous solution at low temperatures, although they also suggested that the stability of the system could be improved by lyophilization. The authors concluded that the lyophilized formulation preserved almost its full transfection potential when aged just below the glass transition temperature of a sucrose matrix (*see* page 1423, 1st ¶). Importantly, the authors also stated that their findings were strictly speaking only applicable to the specific polyplexes they used, *i.e.*, PDMEAMA-pCMV lacZ plasmid complexes, although their results might be extended to other polyplex and lipoplex formulations (*see* page 1423, 2nd ¶). Cherng did not in any way teach or suggest a plasmid attached to inert metal carrier particles, much less such particles obtained in the presence of a homopolymer of arginine and metal ion chelating agent.

Instead, at best, a skilled person reading Cherng might have been motivated to modify and possibly improve on the stability of DNA in the context of polyplexes and lipoplexes formulations, but certainly not inert metal carrier particles having DNA attached on their

surface, much less exhibit increased stability upon using a homopolymer of arginine and a metal ion chelating agent.

Even if a skilled person was to combine the teachings of Cherng with other cited documents, he/she would not have expected that a combination of a homopolymer comprising Arg_2 to Arg_{10}, together with DNA, particles and a chelating agent, *e.g.*, EDTA, could have improved the physical attachment of DNA to the particles or improved the stability of the composition, thereby making it suitable for use as per the present invention. Thus, the cited references, alone or in combination, cannot render the present claims unpatentable.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Sanford and Balhorn as evidenced by Oard and in further view of Cherng and Barman

Claims 1-7, 12-46 and 67-71 were rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Sanford and Balhorn as evidenced by Oard and in further view of Cherng and Barman (U.S. Pat. Appl. Publ. No. 2004/0142475). Applicants respectfully traverse this rejection for at least the reasons previously discussed and those that follow.

Barman described a composition for delivery and a gradual/controlled release of bioactive agents (such as a peptide, protein and/or nucleic acid coding for, *e.g.*, HBV antigen) into cells (*e.g.*, phagocytes), where the composition comprised microparticles that were composed of a delivery matrix made out of an anion or zwiterion compound (*see* ¶¶ [0005], [0040] – [0046], [0104] and [0128] – [0130]). Specifically, the bioactive agents were present in the microparticles (*see* ¶ [0040], first line). In other words, the agents were encapsulated or contained within the microparticles to facilitate their delivery and gradual/controlled release (*see* ¶ [0104]).

In the process of preparing the microparticles, Barman stated that stabilizer compounds or DNA-condensing agents could be included, and Barman provided a long list of possible alternatives including sucrose, but not raffinose (*see* ¶¶ [0041] and [0054]).

According to Barman, the purpose of the stabilizer or DNA-condensing agent was to keep the nucleic acid supercoiled, and thus protected, during encapsulation and throughout the microparticle formation process (*see* ¶ [0046] last sentence).

Accordingly, based on the teachings of Barman, the skilled person would have been aware that adding sucrose, not raffinose, to an anionic or zwiterion compound would protect the biological agent during the process of encapsulation of the agent. There was no teaching in Barman, however, that would have suggested to a skilled person that sucrose, or any of the other disclosed compounds mentioned in ¶ [0041] and [0054], would have had a physical/chemical effect on DNA when the DNA is applied onto the surface of an inert particle.

Moreover, Barman provided no motivation to use a sugar, *e.g.*, sucrose, as per the present invention in light of the fundamentally different environments in which any interactions between the agent and the compound would take place, namely inside a microparticle (encapsulation) versus on the surface of an inert metal carrier particle. In view of the above, even if a skilled person was to combine the teachings of Barman with other cited documents, he/she would not have expected that a combination of a homopolymer comprising Arg_2 to Arg_{10}, together with DNA, inert particles and a chelating agent could have improved the physical attachment of DNA to the particles and thus stability of the composition, thereby making it suitable for use as claimed. Thus, the cited references, alone or in combination, cannot render the present claims unpatentable.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date March 5, 2008

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